REMARKS/ARGUMENTS

The present amendment is submitted in accordance with the *Revised Amendment Format* as set forth in the Notice provided on the USPTO web site for the Office of Patent Legal Administration; Pre-OG Notices; signed 1/31/03.

Claims 1-25 are pending in the application. Claims 1-17 are examined on the merits. No claims are allowed. Claims 18-25 have been canceled without prejudice to subsequent revival. Applicants reserve the right to prosecute claims 18-25 in a divisional application.

Claims 1-4, 7-11 and 15-17 have been amended. Claims 5, 6, 12 and 13 have been canceled. Claims 26-31 has been added. Entry of the amendment, reconsideration of the rejection, and allowance of claims 1-4, 7-11, 15-17 and 26-31 are requested.

The Amendment

In order to expedite prosecution of the application and advance the case toward allowance, the claims have been amended. No new matter was introduced by this amendment.

The specification has been amended to correct for informalities, including notations of numerical values wherein a comma was replaced with a period. The specification was also amended to provide for consistent and correct use of trademarks, wherein the trademarked name was capitalized and is now accompanied by its generic term (*e.g.*, BENZONASE endonuclease).

Claim 1 has been amended to clarify that "virus antigen" is purified, as requested by the Examiner. Support for this amendment can be found on page 6, paragraph [025], line 9. Claim 1 has also been amended to delete the redundant phrase "of cells" and to provide for grammatical consistency. Furthermore, claim 1 has been amended to specify that the harvested virus is filtered with a first and second filter, wherein the second filter has a pore size of between about 0.1 an about 0.5 μm. Support for this amendment can be found on page 7, paragraphs [027] and [028].

Claims 2 and 9 have been amended to provide for proper antecedent basis of the cell culture.

Claims 3 and 4 have been amended to clarify that the "filtering" refers to the "first and second filtering step" in claim 1, respectively. Claim 4 has also been amended to specify that the second filter has a pore size of about 0.2 μm. Support for this amendment can be found on page 7, paragraphs [027] and [028].

Claims 5 and 6 have been canceled.

Claim 7 has been amended to add a reference to cellular protein contaminants and to delete the phrase "at least about 35 fold" in order to clarify the meaning of the claim which refers to reduction of cellular protein and nucleic acid contaminants. Support for this amendment can be found on page 6, paragraph [025].

Claim 8 has been amended to provide for grammatical consistency and to further specify that the harvested virus is filtered with a first and second filter, wherein the second filter has a pore size of between about 0.1 an about 0.5 μm. Support for this amendment can be found on page 7, paragraphs [027] and [028].

Claims 10 and 11 have been amended to clarify that the "filtering" refers to the "first and second filtering step" in claim 8, respectively. Claim 11 has also been amended to specify that the second filter has a pore size of about 0.2 μm. Support for this amendment can be found on page 7, paragraphs [027] and [028].

Claims 12 and 13 have been canceled.

Claim 15 has been amended to provide for proper antecedent basis to the "filtered virus".

Claim 16 has been amended to delete the redundant phrase "said cells".

Claim 17 has been amended to refer to an "immunogenic composition" to comply with the Examiner's suggestion. Support for this amendment can be found on page 16 in Example 3. Applicants state for the record that the immunogenic composition claimed herein is understood to include a composition that elicits a protective immune response upon administration. The claim has also been amended to provide for grammatical consistency and to specify that that the harvested virus is filtered with a first and second filter, wherein the second

filter has a pore size of between about 0.1 an about 0.5 μm. Support for this amendment can be found on page 7, paragraphs [027] and [028].

Claims 18-25 have been canceled.

New claim 26 has been added to specify that the immunogenic composition of claim 17 may further include an adjuvant. Support for this amendment can be found on page 10, paragraph [042], line 2.

New claim 28 has been added to specify that the filtered virus of claim 1 may further be treated with a nucleic acid degrading agent. Support for this amendment can be found on page 8, paragraph [032], lines 1-3.

New claims 27, 29 and 30 specify that the first and second filters (as used in claims 1, 8 and 17) are based on a positively charged matrix and a hydrophilic matrix, respectively. Support for this amendment can be found on page 7, paragraph [027].

New claim 31 indicates that the method of claims 1, 8, or 17 is suitable for large scale production. Support for this amendment can be found on page 3, paragraph [006]; and on page 12, example 1, paragraph [048], line 11; and page 14, paragraph [055], line 2.

Specification

The disclosure is objected to because of the certain informalities such as incorrect notation of numerical values in Tables 1 and 3, Example 3 and paragraph 55. The specification has been corrected accordingly (see "The Amendment", *supra*). No new matter was added by this amendment since the meaning of the numerical values as amended (English notation) is consistent with the original meaning of the numerical values (German notation).

Rejection Under 35 U.S.C. §112

Claims 1-7 and 10-13 have been rejected under 35 U.S.C. §112, second paragraph for being allegedly indefinite.

Herein, the Examiner requests clarification to whether whole virus or virus antigen is recovered in the method of claim 1. Claim 1 has been amended to clarify that the method includes purifying virus antigen (see "The Amendment", *supra*).

Claims 3-6 and 10-13 are rejected because the ranges "between about 0.3 and about 1.5" and "between about 0.1 and 0.5" are allegedly unclear.

This rejection is respectfully traversed.

Filter ranges, such as the ones described herein are clearly understood by those of skill in the art. Thus, it would be unduly limiting to restrict the Applicants to a filter with only one specific pore size. In fact, in light of the instant teaching, the skilled artisan would recognize that a pre-filter (*i.e.,* the filter used in a first filtering step) can have particular pore size ranges and he or she would know what "about 0.3 μm to about 1.5 μm" means in the context of practicing the invention. For example, if the particles to be filtered are slightly larger, the skilled artisan may select a pre-filter with a pore size of 1.3 μm; if the particles are slightly smaller, the skilled artisan may select a pre-filter with a pore size of 0.6 μm, *etc.* Any such selection of pre-filters is well within the knowledge of those of skill in the art. Furthermore, Applicants have determined that the second filtering step can be conducted with a filter at pore sizes "between about 0.1 and 0.5 μm". Herein, Applicants have shown that, surprisingly, filters with pore sizes of less then 0.5 μm are useful for filtering virus particles during a second filtering step to achieve a high purity. Armed with this knowledge the skilled artisan can now determine other suitable pore size ranges that will lead to a highly pure virus filtrate as a result of a second filtering step.

It is also noted that the availability of manufactured filters with specific pore size ranges may change during the life time of the patent. If Applicants are restricted to only one pore size Applicants may be faced with a situation where a specific filter is no longer commercially available which would place an undue burden on the Applicants. Not even to mention, that others would be encouraged to infringe upon Applicants' invention by simply employing slightly different filter pore sizes.

Claims 5-6 and 12-13 have been canceled (see "The Amendment", *supra*).

Claim 7 is rejected because the phrase "at least about 35 fold" lacks comparative basis, as indicated by the Examiner. The term has been deleted from the claim (see "The Amendment", *supra*).

In light of the amendment and the arguments presented above, Applicants respectfully request that the rejection of claims 1-4, 7 and 10-11 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claim 17 is rejected under 35 U.S.C. §112, first paragraph for being allegedly not enabling for making a vaccine.

In the interest of prosecution efficiency, Applicants have amended the claim to refer to an *immunogenic composition* as suggested by the Examiner. However, this amendment is made to advance the claims toward allowance and must not be construed as an acquiescence in the rejection. Rather, the amendment complies with the Examiner assertion that the Applicants are enabled for a method of making an immunogenic composition comprising RRV. The immunogenic composition claimed herein is understood to include a composition that elicits a protective immune response upon administration. Applicants have attached an experimental report by the inventors which clearly shows that immunized mice were challenged and ultimately protected from developing viraemia as a result of immunization with the RRV immunogenic composition of the instant invention (see page 3 of the attached *Experimental Report*).

In light of the above amendment, the rejection is moot and Applicants respectfully request that the rejection of claim 17 under 35 U.S.C. §112, first paragraph, for lack of enablement, be withdrawn.

Rejection Under 35 U.S.C. §103

Claims 1-17 are rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Dubensky Jr. *et al.* (USPN 5,789,245) in view of Yu *et al.* (Vaccine (1997) 15(12/13):1396-1404).

The Examiner indicates that Dubensky's method is drawn to a large-scale production of recombinant alphavirus vectors and that Yu teaches a RRV product that is suitable for eliciting an immune response, which is not a vector. The Examiner further asserts that one would have a reasonable expectation of success that the recombinant aplphavirus vectors of Dubensky and the virus of Yu would have similar production methods; and that it would have been obvious to make the product of Yu with Dubensky's method. It also suggested that one

would have been motivated to make large quantities of RRV for immunogenic compositions and for candidate vaccine research given the lack of treatment for RRV according to Harley *et al.*

To the extent that the rejection applies to the claims as amended, the rejection is respectfully traversed. The claims have been amended to specify that the harvested virus is filtered with a first and second filter, wherein the second filter has a pore size of between about 0.1 an about 0.5 μm.

It is well understood that in order to properly maintain an obviousness rejection, three basic criteria must be met. In fact, MPEP 2143 states the following:

> To establish *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

I. No Motivation To Combine The References:

Dubensky *et al.* (Dubensky) teach the use of *recombinant* viruses as vectors, and more specifically, the use of recombinant alphaviruses which are capable of expressing a heterologous sequence in target cells. As such, the teachings disclosed in Dubensky are focused on techniques of introducing genes into an organism by using an alphaviurs as a shuttle. In contrast, the present invention relates to a method of producing a purfied Ross River Virus (RRV) in order to develop a vaccine against RRV. Clearly, a person skilled in the art would not have been able to arrive at the claimed subject matter based on Dubensky's disclosure. Moreover, the skilled artisan would certainly not have been motivated to consult Dubensky since Dubensky's disclosure relates to an entirely different technical field (*i.e.*, introducing foreign genes into target cells using a recombinant virus as a shuttle) than the instant invention (*i.e.*, vaccine development). Yu *et al.* (Yu) discuss the development of a vaccine against RRV, however, the virus is obtained from an acute phase serum sample of a serologically confirmed patient (page 1118, right column, first paragraph) and is not a recombinant virus. Since Dubensky's teachings relate primarily to recombinant viruses,

the references are not properly combined because there is no motivation in either the references themselves or in the knowledge generally available to one of ordinary skill in the art to combine them (MPEP 2143.01). Moreover, Yu is silent on virus purification, an essential step in vaccine development while Dubensky is silent on virus inactivation. Consequently, the skilled artisan would not have been able to arrive at the present invention based on the disclosure of Dubensky or Yu, neither alone nor in combination with each other.

II. The Cited References Do Not Teach All the Elements of the Pending Claims:

It is also well established that all limitations of the claims must be disclosed by the combination of references cited as the prior art in order to establish *prima facie* obviousness (MPEP 2143.03). The pending claims have been amended to specify that the harvested virus is filtered with a *first and second filter*, wherein the *second filter has a pore size of between about 0.1 an about 0.5 μm*. Dubensky fails to discuss a purification method wherein a second filter has a pore size between about 0.1 and about 0.5 μm and Yu does not even mention filters. Since in each case, all of the claim limitations are not suggested by the combination of references, the rejection should be withdrawn.

Most importantly, the prior art simply does not teach or suggest a second filter with a pore size that is less than 0.5 μm. To maintain the present rejection, the Examiner must explain why one would be motivated to select a small pore size of less than 0.5 μm in light of the teaching of the prior art. Dubensky only teaches a second filter of 0.65 microns and this selection makes sense in light of what is know in the art. One of skill would recognize that virus aggregates would impede filtering if he or she were to select filters with pore size ranges of less than 0.65 microns. Hence, one of skill would not be motivated to select a second filter with *a pore size of between about 0.1 an about 0.5 μm* without the teachings of the instant invention.

Further, Dubensky is silent on the reduction of contaminants by 35-fold resulting in less than about 10 pg of cellular nucleic acid per 1 μg of virus antigen (as the Examiner correctly pointed out on page 7 of the Office Action). However, the Examiner then assumes that the step of adding DNAse in Dubensky's method leads to the same reduction in contaminants as in

Applicants' method, primarily because Applicants optionally use DNAse. The Examiner's misunderstanding must stem from the fact that she assumes that DNAse is mostly responsible for the high purity of the virus antigen in Applicants' method. This is clearly not the case. As is pointed out in the specification on page 7, paragraph [028], the filtering alone removes substantially all cellular protein and nucleic acid contamination resulting in an intermediate pure preparation of at least about 97% compared to the starting virus. Herewith, the inventors have achieved a very pure preparation primarily because of the second filtering step. As discussed above, the second filter has a small pore size of between about 0.1 an about 0.5 μm. Surprisingly, the Applicants found that a filter with this small pore size works. The specification also indicates that Figure 1A impressively shows that filtering removes substantially all VERO cell derived proteins from the Virus preparation. In fact, prior to Applicants' invention it was entirely unpredictable in the art that a small filter range of less than 0.5 μm would lead to such a ***surprisingly clean virus preparation***, mainly because viruses have a tendency to form aggregates thereby clogging the filters which results in a lower virus yield. Besides that, Dubensky is silent on VERO cells grown in serum-free medium (see Office Action, page 6). Thus, Dubensky has ever more reason to use a larger filter pore size (like 0.65 micron) to prevent the clogging of his filter when clarifying crude recombinant alphavirus particles (see column 120, line 13).

Applicants respectfully assert that there would be no conceivable expectation of success by combining Yu and Dubensky, particularly since neither discusses or even suggests a filter range between about 0.1 and about 0.5 μm. Therefore, neither of the references could have taught the superiority of the claimed method.

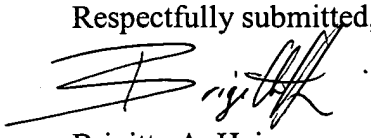
In light of the amendment and the arguments presented above, Applicants respectfully request that the rejection of claims 1-4, 7-11 and 14-17 under 35 U.S.C. §103(a), be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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